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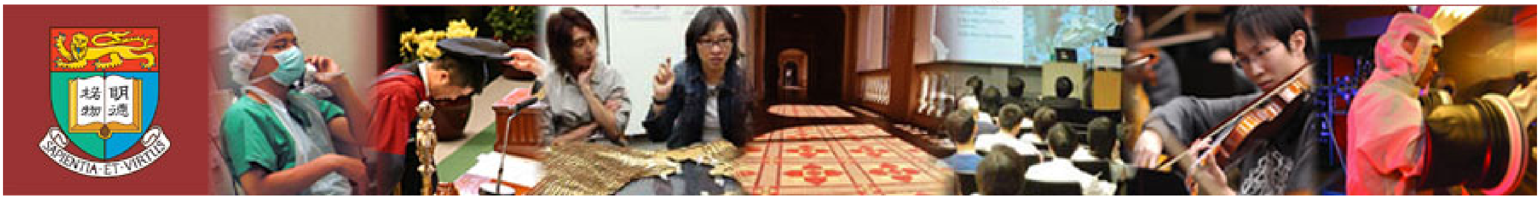

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Effects of high-frequency repetitive Transcranial Magnetic Stimulation (rTMS) on swallowing function of post-stroke individuals with dysphagia: A pilot study

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Abstract

This pilot study investigates the effects of high-frequency 5 Hz repetitive Transcranial Magnetic Stimulation (rTMS) on swallowing functions and quality of life of post-stroke individuals with dysphagia. Two male and two female participants were assigned randomly to active and sham groups. The participants in the active group received ten sessions of active rTMS for two weeks, whereas the sham participants received ten sessions of sham rTMS for two weeks. Outcome measures were taken at baseline, one week and one month post rTMS. The results showed that the active group had higher oropharyngeal efficiency (OPSE) and lower swallowing activity and participation profile (SAPP) total score at one week and one month post-stimulation. The current study suggests that 5 Hz rTMS may help to improve swallowing functions in patients with post-stroke dysphagia.

Effects of high-frequency repetitive Transcranial Magnetic Stimulation (rTMS) on swallowing function of post-stroke individuals with dysphagia: A pilot study

Dysphagia, which refers to the difficulties in preparation, control and/or transportation of food from the oral cavity to the stomach (Logemann, 1998), is a common health problem after stroke with reported incidence as high as 78% (Teasell, Foley, Fisher, & Finestone, 2002; Martino et al., 2005). The presence of dysphagia is associated with chest infection, dehydration, malnutrition (Foley Martin, Salter, & Teasell, 2009), as well as anxiety and depression (Eslick & Talley, 2008). Despite this, efficacy of dysphagia treatments is controversial as limited evidence-based randomized clinical trials were done to support any post-treatment changes (Logemann, 2012). Application of non-invasive repetitive transcrainal magnetic stimulation (rTMS) as possible management for dysphagia has been the interest of researchers in recent years (Verin & Leroi, 2009; Khedr, Abo-El Fetoh, & Rothwell, 2009; Khedr & Abo-El Fetoh, 2010). However, the site and frequency of rTMS vary in these studies and the optimal protocol of rTMS remains uncertain. Further studies are needed to explore the potential benefits of rTMS on dysphagia. The current study aims at investigating the effects of high-frequency 5Hz rTMS over the tongue motor cortex on swallowing functions of individuals with post-stroke dysphagia.

The tongue is important for food bolus control and propulsion in oral phase of swallowing. Given its importance in swallowing, improvements in tongue motor functions should lead to improvements in swallowing functions. Researchers have studied the effects of tongue exercises on swallowing functions of stroke individuals. Robbins et al. (2007) found that an eight-week lingual resistance exercise program resulted in increased lingual isometric and swallowing pressure and improved swallowing function in ten stroke patients. Yeates, Molfenter, and Steele (2008) reported increased tongue strength and tongue pressure accuracy, as well as improved bolus control in three post-stroke dysphagic individuals who received tongue-pressure training. Although these studies suggested that tongue training programs, which resulted in improved tongue strength and movement, may improve swallowing function in stroke individuals, the power of the studies were limited by the small sample size and non-controlled design. Moreover, tongue-strengthening exercises may require regular practices without supervision from speech therapists. Consequently, the efficacy of exercises depends largely on the motivation and persistence of patients. Another limitation of these exercises is that they require following of instructions, which may be difficult for patients who are cognitively impaired.

As such, researchers investigated alternative treatment options for dysphagia in recent years. Repetitive transcranial magnetic stimulation is one of them. Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that modulates brain cortex using electromagnetic field induced by an alternating current (Bailey, Karhu, & Ilmoniemi, 2001; Butler & Wolf, 2003). The induced current depolarizes nerve cells, which consequently disrupts or stimulates brain activity (Barker, 1991). Since mid-1990s, repetitive TMS (rTMS) has been investigated as treatment for depression and in recent years it is approved for clinical use in US (Fitzgerald & Daskalakis, 2011). Apart from psychiatric applications, the use of rTMS has been studied in other pathological populations. Positive results have been found in using rTMS to improve limb motor functions (Di Lazzaro et al., 2006; Quartarone et al., 2005) and language functions (Barwood et al., 2011) in stroke patients, and speech intelligibility in Parkinson's disease patients (Murdoch, Ng & Barwood, 2012).

There are two major approaches of rTMS applications. High-frequency (higher than 1Hz) rTMS excites whereas low-frequency (1Hz or lower) rTMS inhibits neural activities. Improved swallowing function was observed in both approaches on unilateral stroke individuals (Park, Oh, Lee, Yeo & Ryu, 2012; Verin & Leroi, 2009; Khedr, Abo-El Fetoh, & Rothwell, 2009; Khedr & Abo-El Fetoh, 2010). Park et al. (2012) investigated the effect of high-frequency rTMS (5Hz) over pharyngeal motor cortex of unaffected hemisphere whereas Khedr and colleagues (2009; 2010) investigated the use of high-frequency rTMS (3Hz) on esophageal cortical area of the affected hemisphere of post-stroke dysphagic patients. All studies found significant clinical recovery from dysphagia. Verin and Leroi (2009) studied application of low-frequency rTMS (1Hz) on mylohyoid cortical area of unaffected hemisphere of chronic dysphagic patients and found improvement in swallowing functions.

However, no objective instrumental measurements on swallowing physiology were used to evaluate the treatment outcomes in these studies. The study by Verin and Leroi (2009) was a non-controlled one which limited its external validity. Although the studies by Khedr and collegues (2009; 2010) and Park et al. (2012) employed randomized controlled procedures, their results have to be interpreted with caution. These studies recruited individuals with acute stroke as participants. The spontaneous recovery from acute stroke might have contributed to the positive results. In sum, the efficacy of using rTMS as treatment for dysphagia is still under investigation.

Given past studies on tongue strengthening exercises and their potential positive influences on improving swallowing functions, the target stimulation site in the current study is the tongue region of the affected motor cortex. The rTMS protocol is adapted from the study by Murdoch et al. (2012), in which significant improvements were found in lingual kinematics after application of 5 Hz rTMS over tongue area of the motor cortex. High-frequency rTMS is used in the current study to increase cortical excitability of the target region because significantly reduced cortical activation was found in hemispheric and brainstem stroke patients with dysphagia (Teismann et al., 2011).

The current study is a pilot study that aims at investigating the short-term effects of 5Hz rTMS on swallowing functions of individuals with chronic post-stroke dysphagia. It contributes to the understanding of possible new management option for post-stroke dysphagia.

Methodology

Participants

Two males and two females (mean age = 71 years old) with chronic dysphagia after stroke were included. Each of them underwent a screening procedure and magnetic resonance imaging (MRI), in which the site of brain lesion was confirmed by a radiologist, before the baseline assessment. All participants were at least two year post-stroke, and were medically stable, cognitively capable to follow instructions and able to sit upright without support. They had impaired tongue and swallowing functions as revealed by oromotor assessment and clinical swallowing assessment carried out by a speech and language pathologist. They had no history of neurological disease other than stroke, pre-existing dysphagia before stroke and/or oromaxillofacial surgery that involves the lips and/or tongue. No personal or family history of seizures or epilepsy, magnetic or other implanted devices, serious medical conditions such as heart disease, and/or on medications that lower neural thresholds was reported from the participants. This study was approved by the Institutional Review Board and informed consents were obtained from all participants. Table 1 lists the background and stimulation information all participants in the current study.

Table 1. *Background and Stimulation Information of All Participants*

Participant (Gender/Age in years)	**Year post-stroke**	**Lesion site as confirmed by radiologists**	**rTMS stimulation site and intensity**	**Current diet**	**Dysphagia symptoms**
Active 1 (Male/ 72)	9	Right cerebellar lesion	Left tongue motor cortex 55%	Pureed meat soft rice diet, medium thick fluid	▪ Prolonged oral transit of honey-thick fluid and pudding
Active 2 (Male/ 76)	5	Right parietal infarct, left frontal lobe lesion	Right tongue motor cortex 55%	Regular diet, thin fluid	▪ Oral residue after swallowing cracker
Sham 1, Active 3 (Female/ 67)	3 (With past history of nasopharyngeal cancer)	Left upper medulla infarct	Left tongue motor cortex 55%	Soft diet, thin fluid	▪ Prolonged oral transition when swallowing cracker
Sham2, Active 4 (Female/ 70)	6	Bilateral parietal infarcts, right thalamic infarct	Left tongue motor cortex 55%	Soft diet, thin fluid	▪ Oral residue

Note. Active 2 was stimulated on the unaffected hemisphere because the lesion site was massive. To avoid medical complications, the unaffected left hemisphere was targeted instead.

Procedures

The current study employed a double-blind, randomized-placebo-controlled research design. Participants were randomly assigned to the active group (n=2) and the placebo group (n=2). Participants and assessors were unaware of the group assignment. The active group received ten sessions of active rTMS whereas the sham group received ten sessions of sham rTMS. The sham stimulation was performed by placing the same stimulation coil, which was disconnected to the stimulator such that it did not give out magnetic stimulation, on the scalp. All participants received assessment sessions at one week pre-, one week post- and one month post-stimulation. The two sham group participants received active stimulation upon completion of the one month post assessment and were re-assessed at one week and one month after receiving active stimulation

Motor Evoked Potentials (MEPs)

A neuronavigational system, Brainsight^{TM} (Rogue Research, Montreal, Canada), was used to provide real-time visual feedback on the positioning of the stimulation coil over the head during stimulation sessions. This software, together with the participant's MRI markings, were used to locate the target area, which was the tongue area of the primary motor cortex of the affected hemisphere.

To ensure that the stimulation was targeted on the desired tongue motor cortex and that the neuropathway from the cortex to the tongue muscles were intact, the motor evoked potentials (MEPs) of the tongue were obtained before the first stimulation session. The tongue motor cortex was first marked on the scalp by measuring the point that was 9.6cm lateral and 3.6cm anterior to the vertex (Murdoch, et al., 2012). Single TMS pulses starting with 50% power was used to elicit the MEPs. The TMS coil was placed tangentially on the scalp, over the earlier marked tongue cortex area. MEPs of the tongue were recorded by the custom-made bipolar surface electromyography (EMG) electrodes that were connected to the Brainsight™ (Rogue Research, Montreal, Canada). A single EMG electrode was placed on the upper surface of the tongue, on the side that was contralateral to the stimulated hemisphere and approximately 1cm from the tongue tip. Non-toxic edible glue (Cyano-Veneer Fast, Hager & Werken, Duisburg, Germany) was used to attach the electrode to the tongue surface. The resting motor threshold was defined as the minimum stimulus intensity required to elicit five responses of about 50 μV or above in 10 consecutive trials (50% successful MEPs) (Rossini et al, 1994). The power and site of stimulation that elicited the resting motor threshold were recorded and used for later stimulation.

Repetitive Transcranial Magnetic Stimulation (rTMS)

The present study adopted the rTMS protocol developed by Murdoch et al. (2012). High frequency 5 Hz rTMS was applied to each participant in the active group. Each participant received a total of 3000 pulses per session for two weeks (10 sessions). Duration of each session was approximately 30 minutes. Active stimulations were carried out using a Magstim Rapid^2 stimulator (Magstim, Carmarthenshire, UK) and an air-cooled double 70mm stimulating coil (Magstim, Carmarthenshire, UK). The stimulation intensity was at 90% of the resting motor threshold obtained. Sham condition was introduced as control by placing the same stimulation coil, which was disconnected to the stimulator such that it did not give out magnetic stimulation, on the scalp. A separate figure of eight, 70mm diameter stimulation coil (Magstim, Carmarthenshire, UK) was connected to the TMS system and used to produce the audible click. All participants were not able to see the coils, the TMS and the Brainsight^{TM} (Rogue Research, Montreal, Canada) systems.

Outcome Measurements

During the screening process, clinical swallowing examination was carried out by a speech and language pathologist to evaluate their current swallowing function. Each participant was asked to swallow three trials of food with four different consistencies, including 10ml thin liquid, 10ml thickened liquid (honey consistency), 10ml paste and a small cookie. Symptoms of dysphagia were recorded.

Each participant undertook one baseline assessment (one week before stimulation) and two post-stimulation assessments (one week and one month post-stimulation respectively). The three components of each assessment were: 1) tongue pressure assessment, 2) Swallowing Activity and Participation Profile (SAPP) and 3) the videofluoroscopic swallowing study.

Tongue pressure assessment. The Iowa Oral Performance Instrument (IOPI) was used to measure the peak tongue pressure (P_{max}) under voluntary control. The participants were asked to press the air-filled bulb, which was placed behind the participants' incisors, as hard as possible for three trials.

The Swallowing Activity and Participation Profile (SAPP). The Swallowing Activity and Participation Profile (SAPP) is a validated self-report questionnaire that investigates the quality of life of dysphagic individuals (Chan, Yiu & Ho, 2011). There is a total of 38 items. Four subscales: swallowing impairment, personal, social and emotional subscales, are included in the questionnaire. Each participant was required to complete the questionnaire during each assessment.

Videofluoroscopic swallowing study (VFSS). Videofluoroscopic swallowing study (VFSS) was conducted as an instrumental evaluation to visualize the swallowing process. Each participant was asked to swallow three trials of 10ml thin liquid, 10ml semi-solid (pudding) and 10ml paste respectively upon signals given by the clinician. The lateral views of the oropharynx and larynx were examined. From the VFSS video, the oral transit time, pharyngeal delay time and pharyngeal response time were measured and the oropharyngeal swallow efficiency (OPSE, Logemann, Kahrllas, Kobara, & Vakll, 1989) was calculated. The OPSE is a global measure for swallowing functions, which quantifies the ability to move food bolus from oral cavity and pharynx to the esophagus safely and efficiently (Rademaker, Pauloski, Logemann, & Shanahan, 1994). Percentage changes in oral transit time after stimulation was calculated. The definitions of these terms and the formulas are listed in Appendix A and B.

Data analysis

Bar charts showing maximum tongue strength, total SAPP score, OPSE and percentage changes in oral transit time were made to illustrate the differences between sham and active group. Descriptive analysis was used to analyze the data obtained from the outcome measures.

Results

All participants tolerated the ten-day stimulation without any physical or mental discomforts.

Maximum Tongue Strength

Figure 1 shows the changes in maximum tongue strength as reflected by the maximum tongue pressure measured using Iowa Oral Performance Instrument (IOPI) for all participants over the three assessment sessions. All but one active participant had increase in maximum tongue strength. When compared with baseline, only active 2 showed an increase of 11kPa at one month post-stimulation. For other participants (both active and sham group), the maximum tongue pressure remained relatively stable at one week and one month post-stimulation assessment

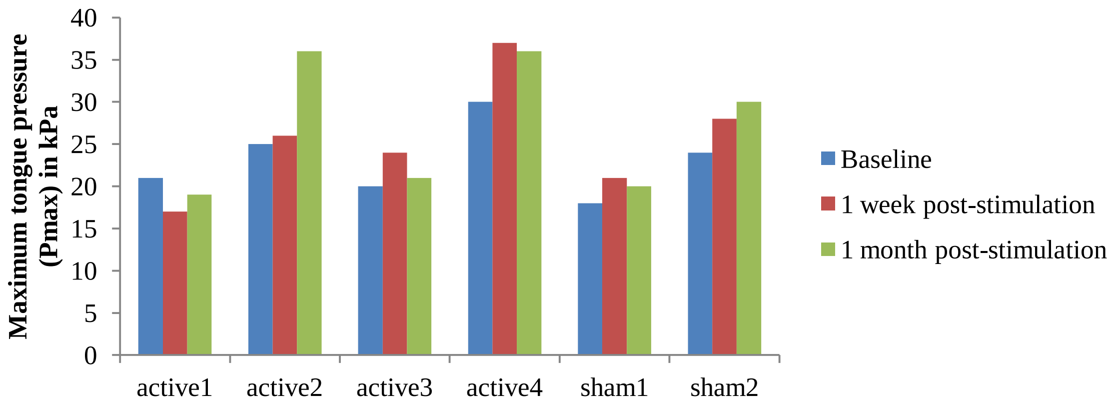

Figure 1. Changes in maximum tongue pressure (in kPa) measured by IOPI

Quality of Life

Figure 2a to 2d show the changes in subscales of Swallowing Activity and Participation Profile (SAPP). The scores of all four subscales decreased in the active group but increased in the sham group after stimulation. For the swallowing impairment subscale, the average score reduced in the active group by 19 and 22 points whereas the average score in the sham group remained stable at one week and one month post-stimulation respectively. For the personal subscale, the average score reduced in the active group by 26 and 22 points whereas the average score increased in the sham group by 5 and 18 points at one week and one month post-stimulation respectively. For the social subscale, the average score reduced in the active group by 19 and 8 points whereas the average score increased in the sham group by 19 and 11 points at one week and one month post-stimulation respectively. Lastly, for the emotional subscale, the average score reduced in the active group by 21 and 20 points whereas the average score increased in the sham group by 2 and 14 points at one week and one month post-stimulation respectively.

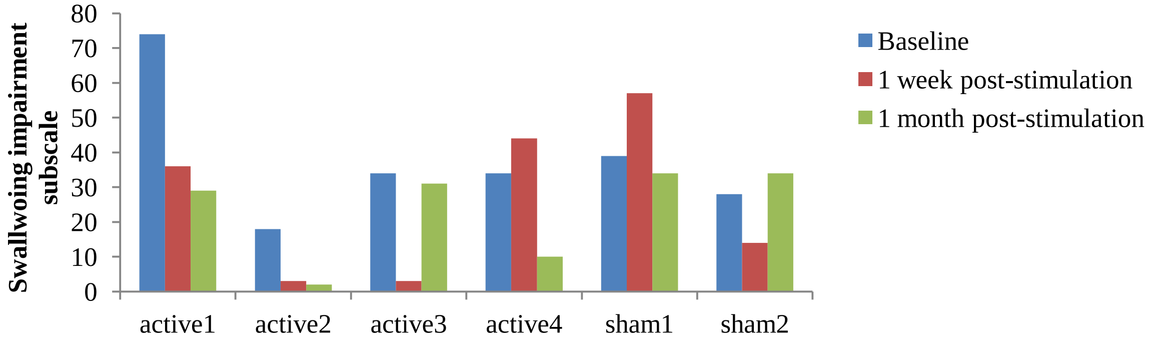

Figure 2a. Changes in swallowing impairment subscale

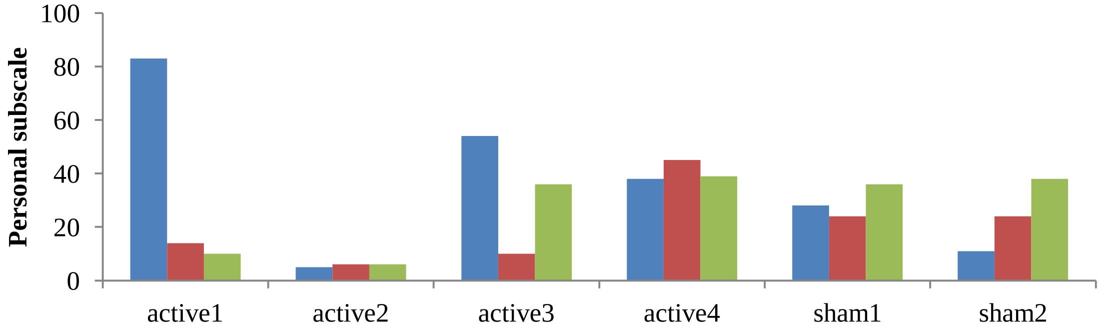

Figure 2b. Changes in personal subscale

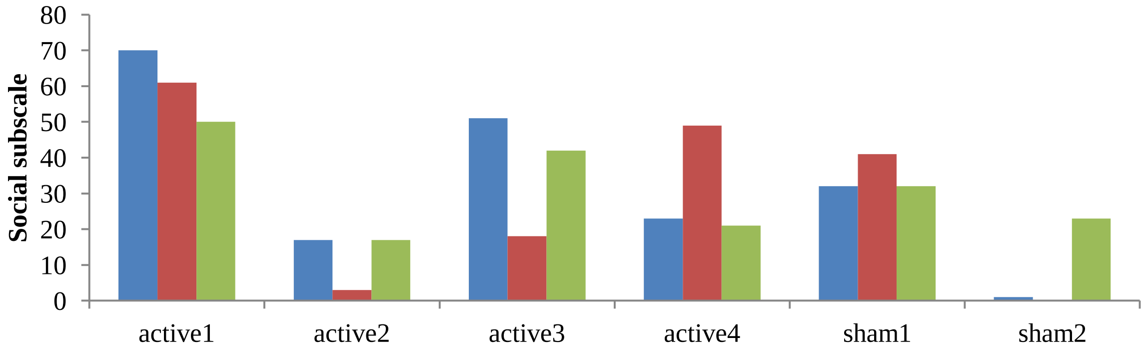

Figure 2c. Changes in social subscale

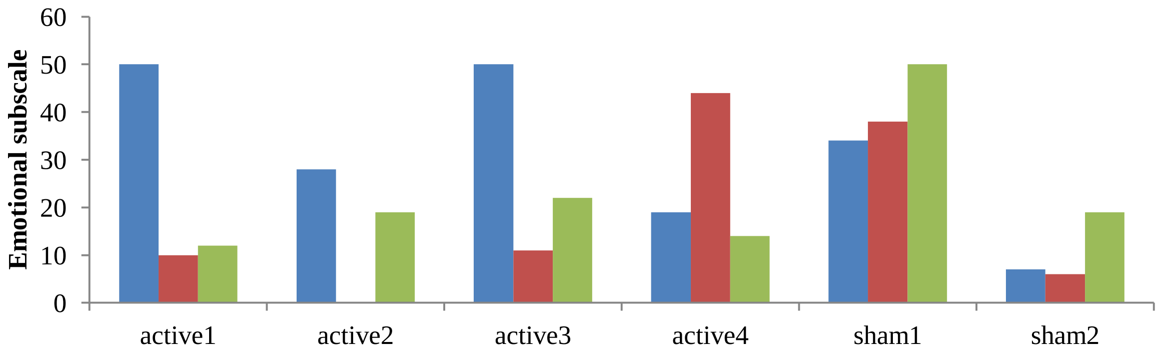

Figure 2d. Changes in emotional subscale

Figure 3 shows the changes in total SAPP scores of all participants over the three assessment sessions. The total SAPP score of all participants in the active group decreased after stimulation. The average reduction is 72.8 and 72 points at one week and one month post-stimulation respectively. For the sham group, the total SAPP scores increased after stimulation, with average increase of 12 and 43 points at one week and one month post-stimulation respectively. The lower the total score, the better the quality of life as perceived by the patients (Chan, et al., 2011).

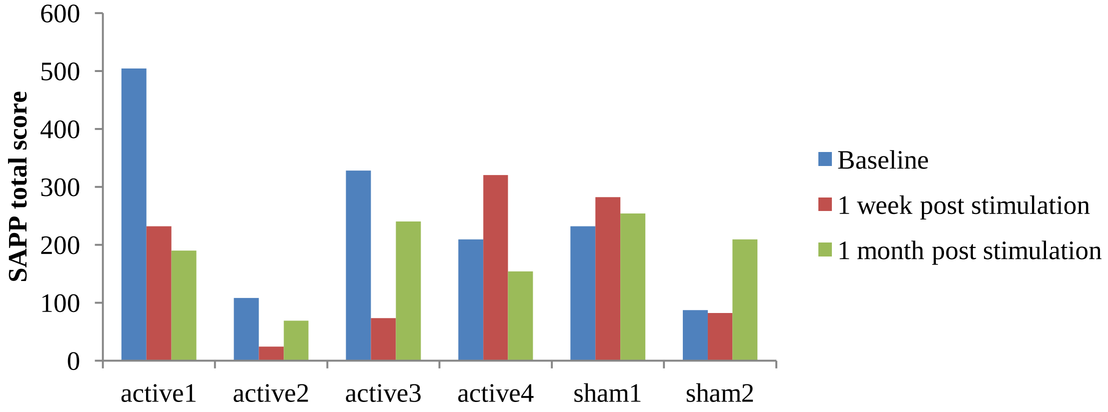

Figure 3. Changes in Swallow Activity and Participation Profile total scores

Oral transit time and Oropharyngeal Swallow Efficiency (OPSE)

Videofluroscopic swallowing study (VFSS) was carried out for three of the participants in the active group and one of the participants in the sham group at baseline and one month post-stimulation. Figure 4 shows the average percentage changes in oral transit time across the three consistencies (thin liquid, honey-thick fluid and paste) after stimulation. The oral transit time increased in the active group but decreased in the sham group after stimulation.

These changes were observed across bolus consistencies.

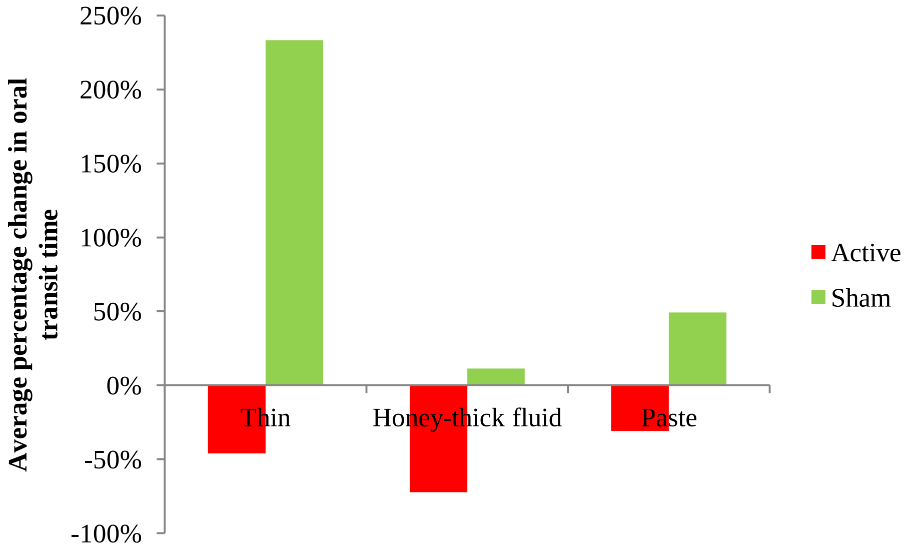

Figure 4. Percentage change in oral transit time across consistencies (thin liquid, honey-thick fluid and paste)

Figure 5a, 5b and 5c show the changes in the OPSE for the three food consistencies across the assessment sessions. For thin liquid, the average OPSE increased by 38 in the active group and decreased by 26 in the sham group. For honey-thick fluid, the average OPSE increased by 22 in the active group and decreased by 5 in the sham group. For paste, the average OPSE increased by 9 in the active group and decreased by 8 in the sham group. An increase in OPSE reflects a more efficient and safer movement of food bolus from oral cavity into the esophagus. The OPSE of non-dysphgic individuals ranges from 78 to 79 (Rademaker et al., 1994; Logemann, Kahrllas, Kobara, & Vakll, 1989).

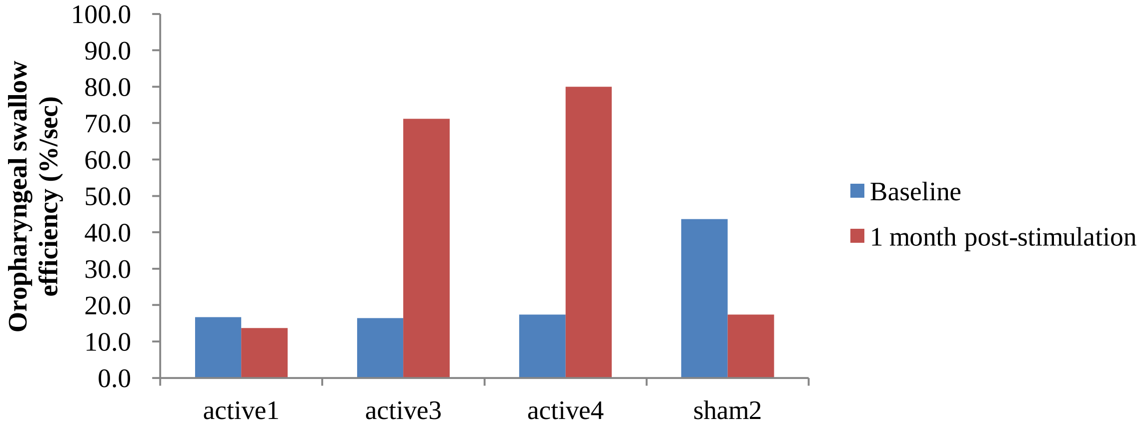

Figure 5a. Changes in oropharyngeal swallow efficiency (%/sec) for thin liquid

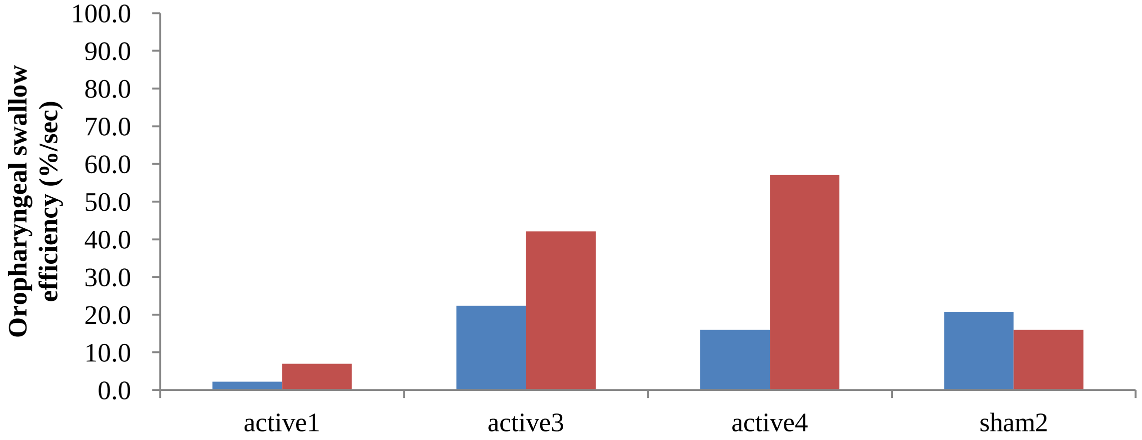

Figure 5b. Changes in oropharyngeal swallow efficiency (%/sec) for honey-thick fluid

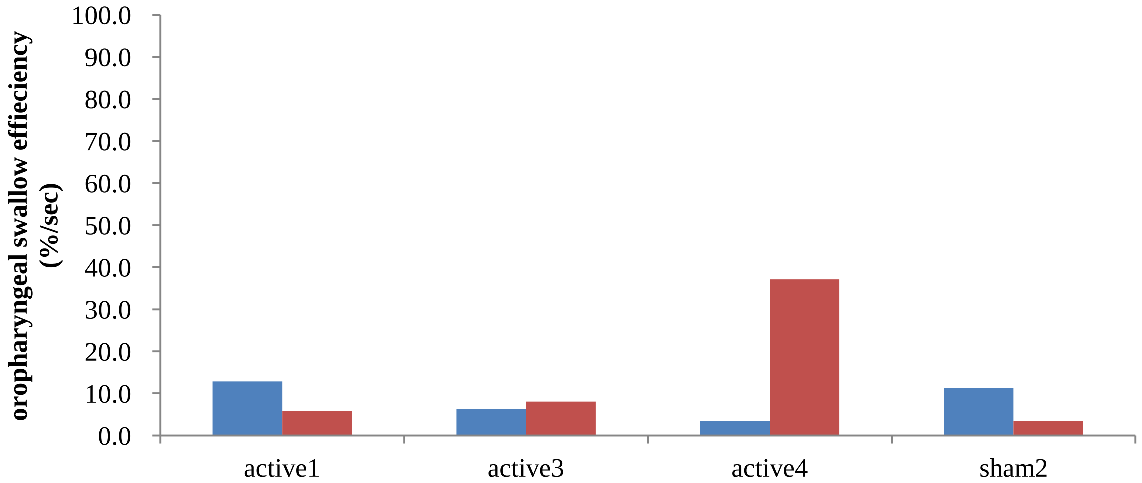

Figure 5c. Changes in oropharyngeal swallow efficiency (%/sec) for past

Note. Active 4 is the same person as Sham 2

Discussions

The present study investigated the short-term effects of high-frequency repetitive transcranial magnetic stimulation (rTMS) on swallowing functions and quality of life of four patients with post-stroke dysphagia. Results showed that there were improvements in oropharyngeal swallow efficiency (OPSE) and quality of life in individuals who received active stimulation, whereas those who received sham stimulation showed no improvements in these areas. The findings suggest that the application of 5Hz rTMS in individuals with post-stroke dysphagia may help to improve swallow functions and quality of life. Moreover, these improvements are maintained up to 1 month after stimulation.

One of the major findings of the current study was the improvements in the OPSE in the active group but not in the sham group. The improved OPSE and the reduced oral transit time suggest that the active group participants were able to swallow more efficiently and safely after active stimulation. It is possible that the reduction in the oral transit time was due to improvements in the tongue movements, which allowed a more efficient bolus clearance from the oral cavity. Since the tongue is crucial in swallowing, especially during the oral phase, where it is responsible for holding and formation food bolus, transition of bolus to pharynx, and clearing oral residue, the improvement in tongue movements may lead to improvements in swallowing function. Moreover, the improvements in swallowing functions were observed across bolus consistencies (thin liquid, honey-thick fluid and paste), which is clinically important as one may encounter different food consistencies in a meal.

Another positive finding from the current study was the improvements in quality of life of the participants who received active stimulation. This is evidenced from the reduction in the SAPP sub-scores and total scores in the active group participants but not those in the sham group. This suggests that the improvement in quality of life is all-rounded. At the impairment level, the participants reported fewer encounters with swallowing difficulties during meals, for example, less frequent choking during meals. It is possible that their personal and social life might also be improved such that they could enjoy the food they loved and felt comfortable having meals with friends and family. Finally, the patients claimed that they felt less embarrassed, anxious and depressed about the swallowing impairments. These changes in self-perception of the swallowing impairments may be a result of improved swallowing functions after application of rTMS. This is an encouraging finding because not only did the instrumental measurement showed improvements in swallowing functions after active stimulation, but the patients also perceived improvement in the quality of life after treatment. As defined by the World Health Organization (1948), “health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (World Health Organization, p. 100), improving one’s quality of life is as important as improving one’s swallowing functions in rehabilitation of post-stroke dysphagia. Despite these encouraging findings, the results in SAPP scores need to be interpreted with cautions because active 3 and active 4 were not blinded to the randomization group. Placebo effects may have contributed to the positive results.

Unexpectedly, there is a lack of observable between-group differences in changes in maximum tongue strength. It was hypothesized that after application of active rTMS, the maximum tongue strength would increase as a result of increased cortical excitability. The dissociation between performances in swallowing functions and tongue strength may suggest that the increase in cortical excitability may result in better tongue movements, but not increasing tongue strength. Muscle strength may depend on active exercises in order to build up muscle mass. It may be possible that increasing tongue strength is better achieved by a bottom-up approach, which involves building up of tongue muscles through isometric exercises. It was found that increased tongue strength is associated with increased tongue volume (Robbins et al., 2007). Future research direction may thus be on whether combination of tongue isometric exercise and rTMS can maximize oropharyngeal dysphagia rehabilitation.

Recommendations for further studies

The current study suggested that the tongue motor cortex is a feasible target for application of 5 Hz rTMS in individuals with post-stroke dysphagia. The advantage of targeting the tongue area over the pharyngeal area is that it causes less discomfort when obtaining motor evoked potentials and determining the stimulation intensity. Targeting on pharyngeal area involves nasal insertion of surface electrodes onto the thenar muscle (Park et al, 2012), whereas targeting on tongue area involves placement of electrodes on tongue surface. Our experiences showed that the participants tolerated the tongue electrodes during the procedures of taking MEPs. Thus, the tongue motor cortex can be the stimulation target for further studies on rTMS in dysphagia rehabilitation.

Although the present study demonstrated encouraging positive results in improving swallowing functions and quality of life in post-stroke dysphgaic patients, the neuromodulations that leads to the improvements are unknown. A possible explanation for the improvements in swallowing functions is the changes in neuromechanism after application of excitatory, high-frequency rTMS. Increase in cortical excitability by application of 5Hz rTMS may increase stimulation to the motor neurons in the corticobulbar and corticospinal tracts, which enhances the synaptic innervations that project to the tongue muscles, leading to more coordinated tongue movements and subsequently more efficient swallowing functions. Further investigations on neurological changes after stimulation are needed to delineate the underlying neuromechanism of the observed improvements. Functional imaging techniques may provide information about neurological activities of the cortex during swallowing. Obtaining MEP of the tongue after stimulation may also provide evidences on the neuromodulations occurred.

Limitations

One of the limitations of the current study is the small sample size. Only four patients were included in the study, in which only two of them received sham stimulation. This would affect the external validity. Although between-group differences were found, the small number of participants made it difficult to generalize the differences to a larger population. Another limitation concerns the selection of patients. In the current study, all but one patient had mild oropharyngeal dysphagia. The post-treatment improvements of these patients may be less obvious than those with moderate or severe dysphagia. Moreover, the duration of follow-up assessment is too short in the current study. Due to time constraints, effects of rTMS were only monitored up to one month post-stimulation. The maintenance of the observed improvements remained uncertain. Whilst immediate effects are important in studying efficacy of new treatments, the maintenance of the effects provide clues on whether the treatment can benefit the patients in long run. Thus, follow up assessments in one or two years after stimulation may be targeted in future investigations.

Conclusions

The results of the current study suggest that the application of high-frequency 5 Hz rTMS over the tongue area of the motor cortex of affected hemisphere could improve tongue movements and functions, which consequently lead to improvements in swallowing functions and the quality of life. All participants tolerated the ten-day rTMS sessions well without discomforts. The present study provided a new insight on the stimulation target of rTMS, which is the tongue area of the primary motor strip of the affected hemisphere.

Acknowledgement

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Appendix A. Formula of oropharyngeal swallow efficiency (OPSE)

Oropharyngeal swallow efficiency (OPSE, Logemann, Kahrllas, Kobara, & Vakll, 1989) was calculated for analysis of VFSS videos. OPSE is calculated with the formula below:

$$\mathrm{OPSE} = \frac{100\text{- }(\mathrm{ORES} + \mathrm{PRES} + \mathrm{ASPB} + \mathrm{ASPD})}{\mathrm{OTT} + \mathrm{PDT} + \mathrm{PRT}}$$

Where,

ORES = approximate percent of bolus remaining in the oral cavity

PRES = approximate percent of bolus remaining in the pharynx

ASPB = approximate percent of bolus aspirated before swallow

ASPD = approximate percent of bolus aspirated during swallow

OTT = oral transit time, the duration (in seconds) between the onset of bolus movement in oral cavity and the arrival of the bolus at the intersection point of the lower rim of mandible and tongue base

PDT = pharyngeal delay time, the duration (in seconds) between the arrival of the bolus at the intersection point of the lower rim of mandible and tongue base and the first laryngeal elevation

PRT = pharyngeal response time, the duration (in seconds) between the first laryngeal elevation and the complete passage of bolus tail through the cricopharyngeal region

(Rademaker et al., 1994)

Appendix B. Formula for calculating percentage change in oral transit time

$$\frac{\text{Post-stimulation OTT - Baseline OTT}}{\text{Baseline OTT}} \times 100\%$$

Where,

OTT = oral transit time, the duration (in seconds) between the onset of bolus movement in oral cavity and the arrival of the bolus at the intersection point of the lower rim of mandible and tongue base